with positive slope but their salts with small anions yield linear plots with negative slope.

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CONFIGURATIONS OF POLYPEPTIDE CHAINS WITH FAVORED ORIENTATIONS AROUND SINGLE BONDS: TWO NEW PLEATED SHEETS

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In recent papers we have described several configurations of polypeptide chains with interatomic distances, bond angles, and other structural features as indicated by the studies in these Laboratories of the structure of crystals of amino acids, simple peptides, and related substances, and have presented evidence for their presence in synthetic polypeptides, fibrous proteins, and globular proteins.[1-9] The requirements that we have imposed for a satisfactory polypeptide configuration, in addition to the correct bond distances and bond angles, are that each amide group be planar, with either the cis configuration or the trans configuration about the C′—N bond (which has nearly 50 per cent double-bond character), and that each carbonyl and imino group (except for proline or hydroxyproline residues) be involved in the formation of a hydrogen bond with N—H···O distance approximately 2.8 A and with the oxygen atom nearly on the N—H axis. The only other structural parameters involved in a configuration of polypeptide chains are the orientations around the N—C and C—C′ single bonds. In the following paragraphs we discuss the question of the relative stability of structures with different values of these orientational parameters.

We are interested in the potential function for orientation around a single bond between the α carbon atom, which forms three single bonds in addition to the bond under consideration, and either the nitrogen atom, which forms a single bond to its hydrogen atom and a bond with somewhat less than 50 per cent double-bond character to the amide carbon atom, or the carbon atom C′, which forms a bond with oxygen which has somewhat more than 50 per cent double-bond character and a bond with nitrogen with

somewhat less than 50 per cent double-bond character. We shall discuss only polypeptides containing residues with the L configuration. The potential function would be expected to have six minima, approximately 60° apart, and six maxima. If the three single bonds on the α carbon atom were equivalent and the two bonds formed by the other atoms were equivalent, as for example in nitromethane, $H_3C—NO_2$, the potential function would have the form shown in figure 1 (*a*), with equivalent minima and equivalent maxima. For propylene, $H_3C—CH=CH_2$, the potential function has either the form shown in figure 1 (*b*) or that in figure 1 (*c*); either the minima are divided into non-equivalent sets of three each, or the maxima are so divided. Curve *1b* corresponds to the situation in which the stable configurations are those with one of the bonds of the α carbon atom coplanar

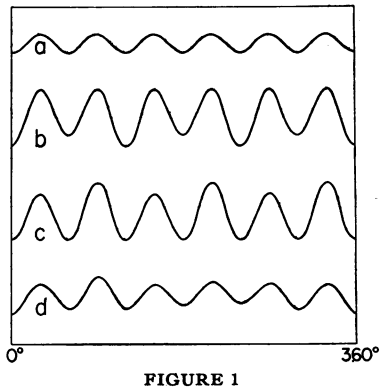

FIGURE 1

Forms of the potential function for orientation around a single bond connecting a tetrahedral carbon atom to a planar group.

with the $CH=CH_2$ group (the two sets representing the configuration cis to the double bond and trans to the double bond, respectively) and curve *1c* represents the situation in which the stable configurations are those with one of the single bonds of the α carbon atom in a plane normal to the plane of the $CH=CH_2$ group.

The height of the potential hump for nitromethane has been independently determined by three investigators, by measurements of heat capacity and of entropy,[10-12] their average value being 0.6 kcal. mole^{-1} (Pitzer and Gwinn, 0.8 kcal. mole^{-1}; DeVries and Collins, 0.6 kcal. mole^{-1}; Jones and Giauque, 0.5 kcal. mole^{-1}). For propylene the height of the potential hump is larger; the value 0.8 kcal. mole^{-1} or less originally suggested by Pitzer[13] has been replaced by the value 2.1 kcal. mole^{-1}, which is supported by several other investigators.[14-17] In neither case have the thermodynamic

data provided a choice between the alternatives represented by curves *1b* and *1c*. For the bonds that we are considering all of the maxima and all of the minima would be different, and the potential function would be expected to have a form such as that shown by curve *1d*.

It seems reasonable to expect that the average energy differences of the maxima and minima for an amide would be somewhere between 0.6 kcal. mole^{-1} and 2.1 kcal. mole^{-1}, perhaps about 1.0 kcal. mole^{-1}, with considerably smaller differences among the minima themselves. This energy quantity, 1 kcal. mole^{-1}, is sufficiently large to cause configurations represented by the minima in the curve to be significantly favored over those represented by the maxima. On the other hand, in crystals of amino acids and related substances in which hydrogen bonds, with energy as great as 8 kcal. mole^{-1}, are formed the metrical requirements might be such that the most stable structure, involving the best conditions for hydrogen-bond forma-

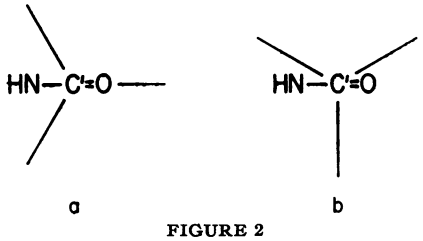

FIGURE 2

A diagrammatic representation of two possible stable orientations of the bonds of the α-carbon atom with respect to the plane of the amide group. The αC atom is directly beneath *C'*; an adjacent single bond (tapered lines) of the αC atom lies either (*a*) in the plane of the amide group or (*b*) in the plane perpendicular to it.

tion, is one in which the molecule is distorted by rotation around the single bonds to the α carbon atom into a configuration of instability with respect to the orientational potential functions. With proteins in an aqueous environment the effective energy of hydrogen bonds is not so great, inasmuch as the difference between the energy of the system with N—H$\cdots$O hydrogen bonds surrounded by water and a system with the N—H group and the O atom forming hydrogen bonds with water molecules may be no more than about 2 kcal. mole.$^{-1}$ Hence the favored orientations around the bonds to the α carbon atoms may be of more frequent occurrence in proteins than in simple amides.

The first question to be answered is whether the adjacent single bond on the α carbon atom lies in the plane of the amide group or in the plane perpendicular to this plane (Fig. 2). The evidence from the known structures

of simple substances is not conclusive, but indicates that the stable configuration is the coplanar one. In N-acetylglycine[18] the bond from the α carbon atom to the carboxyl carbon is very nearly coplanar with the amide group, the carboxyl carbon lying cis to the N—H group. In β-glycylglycine[19] the same configuration is shown by the carboxyl carbon atom and the amide group. In addition, in each of these two substances the carboxyl group itself lies in the same plane as the amide group (to within 0.03 A in β-glycylglycine), so that the single bond from the amide nitrogen atom to the α carbon atom has assumed a coplanar orientation with respect to the carboxyl group. In the benzyl penicillinate ion[20] the bond between the carbon atom of the benzene ring and the α carbon atom adjacent to the carbonyl carbon atom of the amide group is coplanar with the amide group, and trans to the C=O group. There is also a carbon-carbon single bond involving the α carbon atom attached to the nitrogen atom of the amide group that is coplanar with the amide group, and cis to the N—H group; the significance of this orientation is decreased, however, by the fact that this carbon-carbon bond is part of a four-membered ring. In β-glycylglycine, on the other hand, the amino nitrogen atom is rotated by 27° out of the plane of the amide group. We consider it likely that this corresponds to a strained configuration, and that the larger amount of evidence indicating the stability of the orientation corresponding to a coplanar arrangement of one of the single bonds of the α carbon atom and the amide group is to be accepted.

Further evidence is provided by the structures of synthetic polypeptides and proteins. The most common configuration of polypeptide chains seems to be that of the 3.7-residue helix, which we have proposed as representing the structure of synthetic polypeptides,[4] hair, horn, quill, muscle, and related fibrous proteins,[7] and hemoglobin;[9] valuable confirmation of the assignment of this structure to the substances has been provided by Perutz's discovery that the 1.5 A reflection corresponding to the fiber-axis length per residue, which had been observed for porcupine quill, can also be obtained from the plane normal to the helical axis for the other substances.[21] In this helix the C—H bond and the C—R bond (that is, the bond to the β carbon atom of the R group) lie within a few degrees of the plane of an adjacent amide group. In the three-chain structure that we have proposed for collagen and gelatin[8] five of the six C—H and C—R bonds lie very near the planar configuration, the other one being rotated through nearly 30°, presumably into the unfavored configuration to which it is constrained by the nature of the structure.

Accepting the conclusion indicated by the preponderance of the evidence that the minima for the rotational potential functions for the two bonds connecting the α carbon atom with adjacent atoms in the polypeptide chain correspond to coplanar configurations, we give an exhaustive discussion in

the following paragraphs of configurations of this type in which all of the amide groups are of the trans type and are equivalent.

There are six favored orientations about the C—N bond, which we may describe as CH trans to NH, CR trans to NH, CC′ trans to NH, CH cis to NH, CR cis to NH, and CC′ cis to NH. Similarly, we may describe the six favored orientations around the C—C′ bond as CH trans to CO, CR trans to CO, CN trans to CO, CH cis to CO, CR cis to CO, and CN cis to CO. There are accordingly 36 different configurations of the polypeptide chains of L-amino acid residues corresponding to these favored orientations; all 36 configurations are different. They are tabulated below in four groups:

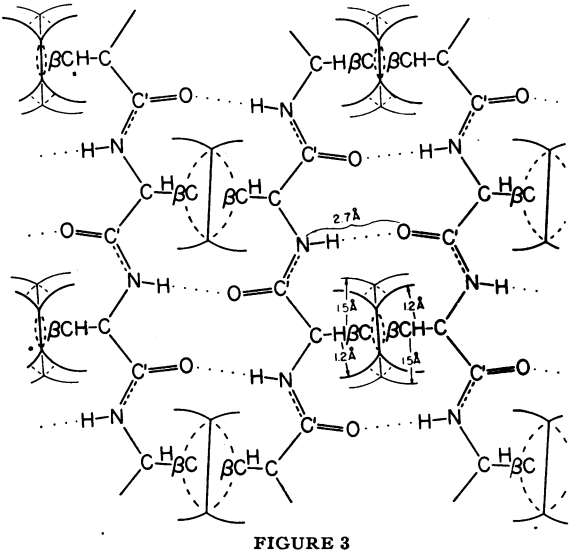

FIGURE 3

A diagrammatic representation of a hydrogen-bonded layer structure of polypeptide chains with alternate chains oppositely oriented, showing steric hindrance between β-carbon atoms of adjacent chains.

trans-trans, cis-cis, trans-cis, and cis-trans. It might be anticipated that the configurations in which CH, CR, or CC′ (or CN) is trans to the bond with the greater amount of double-bond character, of the two bonds once removed, would be either more stable or less stable than the configurations in which one of these bonds is cis to the bond with the greater amount of double-bond character. Accordingly we would expect that either the nine cis-trans structures or the nine trans-cis structures would be somewhat more stable than the other 27 structures; however, the differences in stability are presumably small enough to be unimportant in comparison with the

TABLE 1

CONFIGURATIONS OF EQUIVALENT TRANS AMIDE GROUPS WITH FAVORED ORIENTATIONS ABOUT C—N AND C—C′ BONDS

A. Trans-trans Configurations:
   1. CH trans to NH, CH trans to CO. Pitch 6.68 A, 2 residues per turn. Lateral CO and NH suited to forming the two pleated sheets described below.
   2. CR trans to NH, CR trans to CO. Like 1. Suited to forming the two pleated sheets, but prevented (except for polyglycine) by steric hindrance of R groups.
   3. CC′ trans to NH, CN trans to CO. Ruled out by steric hindrance of NH and O.
   4. CH trans to NH, CR trans to CO. Pitch 6.2 A, 4 residues per turn. Lateral-diagonal CO and NH, suited to forming a tetragonal framework with a = 4.8 A, but prevented by steric hindrance of R groups.
   5. CR trans to NH, CH trans to CO. Like 4.
   6. CH trans to NH, CN trans to CO. Ruled out by steric hindrance of NH and N of adjacent group.
   7. CR trans to NH, CN trans to CO. Like 6.
   8. CC′ trans to NH, CH trans to CO. Ruled out by steric hindrance of O and O.
   9. CC′ trans to NH, CR trans to CO. Like 8.

B. Cis-cis Configurations:
   10. CH cis to NH, CH cis to CO. Ruled out by steric hindrance of NH and O.
   11. CR cis to NH, CR cis to CO. Like 10.
   12. CC′ cis to NH, CN cis to CO. Pitch 7.30 A, 2 residues per turn. Lateral CO and NH, suited to forming the planar sheet with alternate chains reversed in direction, but prevented (except for polyglycine) by steric hindrance of R groups.
   13. CH cis to NH, CR cis to CO. Pitch 5.5 A, 3.7 residues per turn. Axial CO and NH, suited to forming the α helix with intramolecular hydrogen bonds.
   14. CR cis to NH, CH cis to CO. Like 13; the α helix.
   15. CH cis to NH, CN cis to CO. Ruled out by steric hindrance of O and O.
   16. CR cis to NH, CN cis to CO. Like 15.
   17. CC′ cis to NH, CH cis to CO. Pitch 10.4 A, 4 residues per turn. Lateral CO and NH, with H of NH near axis, and CO projecting out. Not suited to formation of intramolecular or intermolecular hydrogen bonds (except possibly for polyglycine only, in a tetragonal framework with a = 4.8 A).
   18. CC′ cis to NH, CR cis to CO. Like 17.

C. Trans-cis Configurations:
   19. CH trans to NH, CH cis to CO. Pitch 5.2 A, 4.8 residues per turn. Diagonal CO and NH, with NH directed toward axis, CO outward. Not suited to formation of hydrogen-bonded sheet or framework.
   20. CR trans to NH, CR cis to CO. Like 19.
   21. CC′ trans to NH, CN cis to CO. Ruled out by steric hindrance of O and O.
   22. CH trans to NH, CR cis to CO. Pitch 8.0 A, 2.8 residues per turn. Not suited to formation of hydrogen-bonded sheet or framework.
   23. CR trans to NH, CH cis to CO. Like 22.
   24. CH trans to NH, CN cis to CO. Pitch 9.6 A, 2.7 residues per turn. Lateral CO and NH, not suited to formation of hydrogen-bonded sheet or framework.
   25. CR trans to NH, CN cis to CO. Like 24.

26. CC′ trans to NH, CH cis to CO. Ruled out by steric hindrance of O and C′ of adjacent amide group.
27. CC′ trans to NH, CR cis to CO. Like 26.

D. Cis-trans Configurations:

28. CH cis to NH, CH trans to CO. Pitch 5.2 A, 4.8 residues per turn (similar to 19). Not suited to formation of hydrogen-bonded sheet or framework.
29. CR cis to NH, CR trans to CO. Like 28.
30. CC′ cis to NH, CN trans to CO. Ruled out by steric hindrance of NH and NH.
31. CH cis to NH, CR trans to CO. Pitch 7.6 A, 2.7 residues per turn. Lateral CO and NH, not suited to formation of hydrogen-bonded sheet or framework.
32. CR cis to NH, CH trans to CO. Like 31.
33. CH cis to NH, CN trans to CO. Ruled out by steric hindrance of NH and adjacent amide group.
34. CR cis to NH, CN trans to CO. Like 33.
35. CC′ cis to NH, CH trans to CO. Pitch 9.5 A, 2.7 residues per turn. Lateral CO and NH. Not suited to formation of hydrogen-bonded sheet or framework.
36. CC′ cis to NH, CR trans to CO. Like 35.

differences due to other structural features. (Note that the orientation trans to CO is trans to the bond with the larger amount of double-bond character, whereas the orientation cis to NH is trans to the bond with the larger amount of double-bond character.)

In table 1 we give for each of the 36 structures, all of which are helical, the pitch of the helix (axial length per turn), the number of residues per turn, the approximate orientation of the CO and NH groups (relative to the helical axis—axial, diagonal, or lateral), and the suitability of the structure to forming hydrogen bonds. Hydrogen bonds may be intramolecular or intermolecular. In the latter case either a hydrogen-bonded sheet or a hydrogen-bonded three-dimensional framework may be formed. A sheet can be formed only when the helix has a twofold screw axis (or a onefold screw axis, which does not occur), and a three-dimensional framework, under our requirements of equivalence of all of the amide groups, only when the helix has a threefold, fourfold, or sixfold screw axis. In describing the configurations we have allowed deviations of a few degrees from the favored orientations around the single bonds, in order to permit the formation of the suitable hydrogen-bonded structures.

From table 1 we see that the only configurations of interest are 1, 12, 13, and 14. The last two configurations represent the α helix, with two different sets of positions of the side chains. Configuration 12, a completely extended polypeptide chain, with identity distance 7.30 A, is suited to the formation of a planar sheet, as shown in figure 3, except that steric hindrance between adjacent chains prevents the formation of this sheet in case that the side chain R is anything but a hydrogen—that is, this planar sheet could be formed only by polyglycine.

The remaining configuration, 1, is of great interest—it seems likely that it is present in many proteins with the β-keratin configuration. The predicted identity distance along the chain axis is 6.68 A, corresponding to 3.34

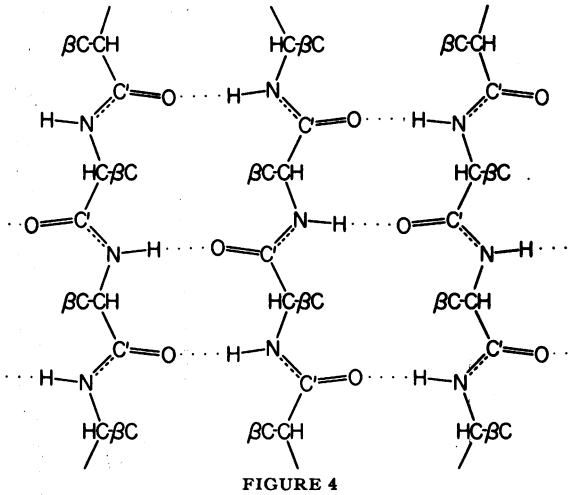

FIGURE 4

A diagrammatic representation of the antiparallel-chain pleated sheet structure.

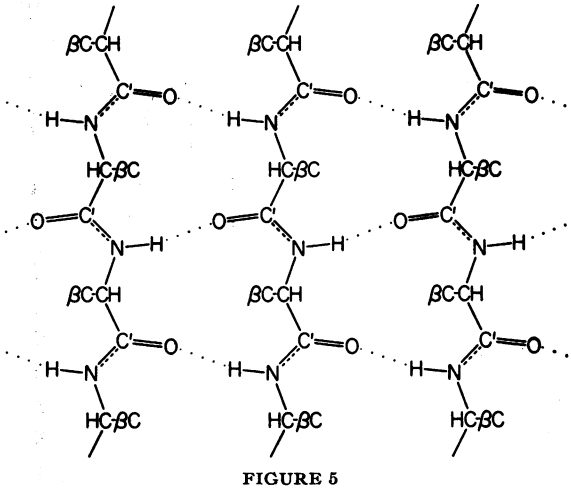

FIGURE 5

A diagrammatic representation of the parallel-chain pleated sheet structure.

A per residue. This agrees very well with the residue length reported by Astbury and Street for proteins with the β-keratin structure, 3.32 A.[22]

We have previously suggested for β keratin a pleated-sheet configuration

of polypeptide chains in which each residue is converted into the following one by the operation of a glide plane of symmetry. With this configuration the orientation around the bonds N—C and C—C′ is not that which we consider to be stable—the stable orientations lead to a residue length in the chain of only 2.84 A, which is not found experimentally for any protein of the β-keratin type. We now think that it is unlikely that this pleated sheet is an important configuration for proteins.

We have found that polypeptide chains with the configuration 1 of Table 1 and residue length 3.34 A can be arranged to form sheets with lateral hydrogen bonds in either one of two ways. In the first way alternate chains in the sheet have opposite directions. The sheet is similar to the first pleated sheet that we described in having α carbon atoms at the same level

TABLE 2

ATOMIC COORDINATES FOR THE ANTIPARALLEL-CHAIN PLEATED SHEET AND PARALLEL-CHAIN PLEATED SHEET

Antiparallel-Chain Pleated Sheet:

Atomic coordinates: $x, y, z;\ \bar{x}, {}^1/_2 + y, \bar{z};\ {}^1/_2 - x, \bar{y}, z;\ {}^1/_2 + x, {}^1/_2 - y, \bar{z}$.

$a_0 = 9.46$ A

$b_0 = 6.68$ A (direction of chain axis)

$c_0 = 1$ A (arbitrary)

Parallel-Chain Pleated Sheet:

Atomic Coordinates: $x', y, z;\ \bar{x}', {}^1/_2 + y, \bar{z}$.

$a_0 = 4.73$ A

$b_0 = 6.68$ A

$c_0 = 1$ A

	x	y	z	x'
C	0.009	0.000	−0.94	0.018
N	−0.036	0.184	−0.25	−0.072
C′	0.053	0.316	0.25	0.106
O	0.183	0.293	0.16	0.366
βC	0.044	0.000	−2.39	0.088

in adjacent chains displaced to the front and the rear of the plane of the sheet, so that it is appropriate to describe it as a pleated sheet. We suggest that this sheet be called the antiparallel-chain pleated sheet, the original one being called perhaps the polar pleated sheet, inasmuch as all of the carbonyl groups are oriented in the same direction, either to the right or to the left, the imino groups being oppositely directed.

The second way of arranging the chains of type 1 into a sheet involves parallel chains, which also are arranged to form a pleated sheet. Diagrammatic representations of the antiparallel-chain pleated sheet and parallel-chain pleated sheet are shown in figures 4 and 5, and drawings of these structures in figures 6 and 7, respectively.

Atomic coordinates for the two pleated sheets are given in table 2. The

antiparallel-chain pleated sheet, considered as made of L-amino acid residues, has orthorhombic symmetry, its symmetry elements being a twofold screw axis in the direction of the chains, a twofold screw axis normal to this direction and in the plane of the sheet, and a twofold axis normal to the plane of the sheet. The parallel-chain pleated sheet has only a twofold screw axis in the direction of the chains.

In the parallel-chain pleated sheet the oxygen atom lies nearly in the N—H direction. The deviation from the N—H axis would be zero in case that the bond angle C—N—H were equal to 125°. It is likely that this bond angle is about 116°, and that there is accordingly a bend in the hydrogen bond of about 10°. This is not so great as to lead to significant instability.

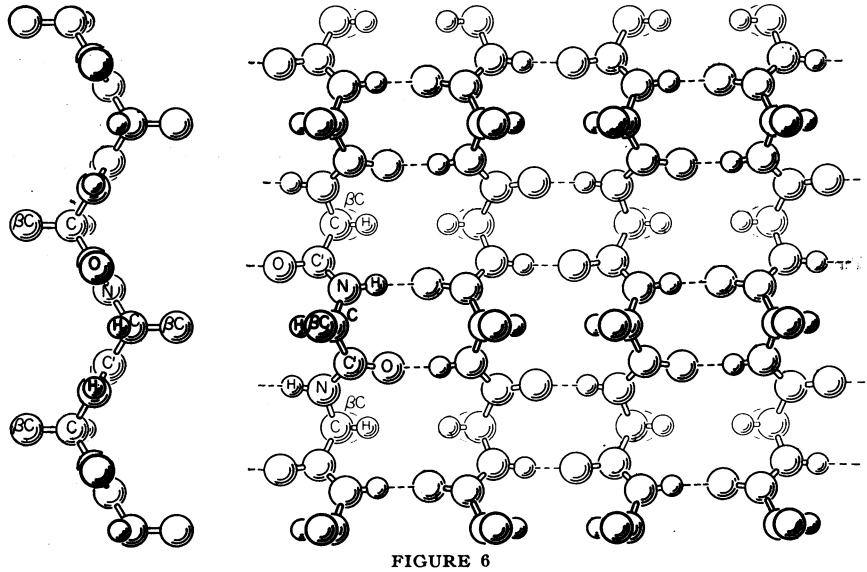

FIGURE 6

Drawing representing the anti-parallel-chain pleated sheet structure.

It is interesting to note that the ability of polypeptide chains with configuration 1 to form lateral hydrogen bonds with either a parallel or an antiparallel adjacent chain strongly suggests that proteins with the β-keratin structure may exist in which there is a randomness in sequence of parallel and antiparallel chains. We plan to discuss this question later, in connection with a comparison of observed and calculated intensities of x-ray reflections for synthetic polypeptides and proteins of the β-keratin type.

It is to be noted that our 5.1-residue helix[1-3] is not represented in table 1, although it satisfies the conditions of containing trans amide groups, and of having all amide groups equivalent. The reason for its failure to appear

as a result of the considerations of the present paper is that it represents unfavorable orientation about both the N—C bond and the C—C′ bond; the orientation about each bond is such as to correspond to a rotation of about 30° for both C—H and C—R from the position of coplanarity with each of the two amide groups adjacent to the α carbon atom. If we accept the assumption expressed above that these orientations represent an instability of about 1 kcal. mole^{-1} relative to the favored orientations, then the 5.1-residue helix would be predicted to be less stable than the 3.7-residue helix by 2 kcal. mole^{-1} per residue. There is no indication from the structures that a corresponding extra stability would be conferred on the 5.1-residue helix by, for example, the presence of N—H···O hydrogen bonds of abnormally great stability, the absence of steric hindrance between side

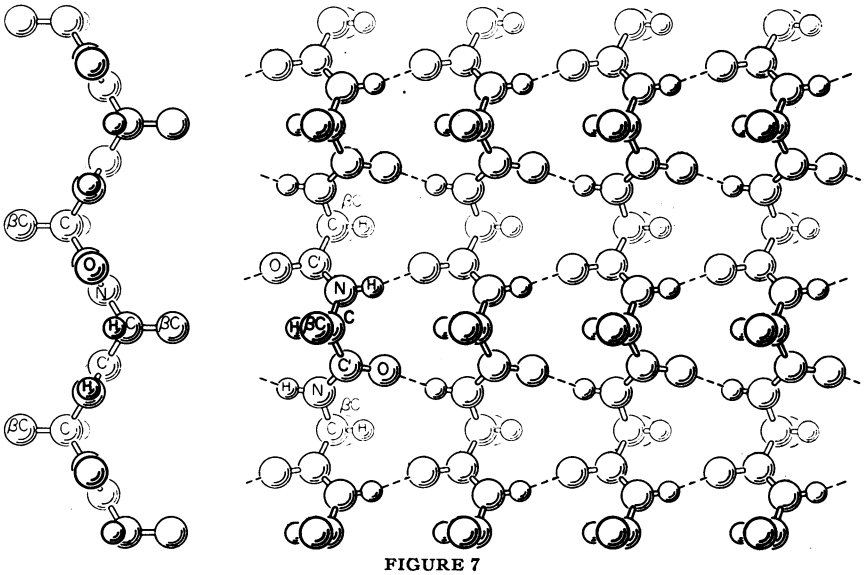

FIGURE 7

Drawing representing the parallel-chain pleated sheet structure.

chains of adjacent turns of the helix which might be present in the 3.7-residue configuration and make it less stable, or any other structural feature—indeed, as was pointed out in an earlier paper,[23] the cylindrical cavity down the center of the 5.1-residue helix would be expected to lead to an extra instability for this configuration by decreasing the intramolecular van der Waals attraction. We thus are led to the conclusion that the 5.1-residue helix is a less stable configuration of polypeptide chains than the 3.7-residue helix, and that it would not be expected to occur very often as an important feature of the structure of proteins. In particular, we are provided with grounds for withdrawing our tentative suggestion[7] that pro-

teins of the α-keratin type undergo transformation to the 5.1 residue configuration on supercontraction. This suggestion was made because the amount of contraction involved in the change from the 3.7-residue helix to the 5.1-residue helix, about 35 per cent, is just that reported to occur in the process of supercontraction. We now think that it is likely that, as suggested by Astbury, the process of supercontraction involves merely a disorientation of α-keratin molecules, without significant change in the configuration of the individual polypeptide chains.

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* Contribution No. 1629.

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